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(54) Title: NON-STEROIDAL ANTI-INFLAMMATORY OPHTHALMIC SUSPENSIONS

(57) Abstract

Topical ophthalmic formulations of non-steroidal anti-inflammatory agents, particularly diclofenac sodium, include an aqueous mixture of the agent in formulations with a pH and concentration of agent that maintains at least a therapeutic amount in suspension and a therapeutic amount in solution.

NON-STEROIDAL ANTI-INFLAMMATORY OPHTHALMIC SUSPENSIONS

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to ophthalmic formulations and more particularly, ophthalmic formulations of non-steroidal anti-inflammatory agents, particularly diclofenac sodium.

Description of the Related Art

Cyclooxygenase is essential in the biosynthesis of prostaglandins which have been shown in many animal models to be mediators of intraocular inflammation. Although sterioidal compounds have been used to treat such inflammation, non-steroidal anti-inflammatory agents, from the group of drugs known as cyclooxygenase inhibitors, have been substituted for steroids because they have not shown the same propensity to produce side-effects in ocular tissues as ophthalmic steroids. Non-steroidal agents are also widely prescribed to reduce pain and inflammation in a wide number of tissues. When used as topical agents in the eye, they suppress inflammatory responses and to prevent particular side-effects of surgical trauma (on the pupil preventing surgical meiosis), fluid accumulating in the back of the eye after cataract surgery (post-surgical macular edema) and the appearance of inflammatory cells and vessel leakage in the anterior chamber. Topical application of non-steroidal anti-inflammatory agents in the eye also appears to relieve some of the itching due to allergic conjunctivitis. Diclofenac sodium, suprofen, and flurbiprofin are non-steroidal anti-inflammatory agents that have been used for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

Anti-inflammatory agents have in the past been administered in solutions at neutral pH. Injection of anti-inflammatory agents in the form of a suspension has also been proposed. Suspensions have been used for topical ophthalmic applications when the drug is not very soluble. However, when the

Formulations of the present invention may be useful for treatment of any condition that may be treated by a non-steroidal anti-inflammatory agent.

Accordingly, it is an object of the invention to provide novel topical ophthalmic formulations containing non-steroidal anti-inflammatory agents.

It is a further object of the invention to provide a novel method of treating the eye.

SUMMARY OF THE INVENTION

One embodiment of the present invention is a topical ophthalmic composition for treatment of the eye comprising an aqueous suspension of a non-steroidal anti-inflammatory agent, the composition having a pH and concentration of agent chosen to ensure that at least some of the agent is in suspension.

The present invention also provides a method for treating diseases of the eye, including inflammation, by topically applying such suspensions to eyes in need of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a composition for treating the eye topically comprising an aqueous mixture of a non-steroidal anti-inflammatory agent, wherein the composition has a pH of about 4.0 to about 8.0, preferably about 5.0 to about 6.8, and at least some of the agent is maintained as a reservoir established in suspension at the pH of the formulation. The amount established in suspension may vary depending on therapeutic needs but it will be at least an amount sufficient to have a therapeutic effect on the eye upon delayed release from the suspension over a period of time. A sufficient amount of agent will also be present in solution to have an immediate therapeutic effect upon topical ophthalmic application. Typically, about 80% to about 90% of the total agent contained in the mixture will be in suspension, but this may vary depending on how much of the agent is desired for delivery and the duration of delivery

TABLE 1

Percent Diclofenac Sodium in Suspension				
pH	Concentration of Diclofenac Sodium in the Formulation .001	.01	.1	1.0
3.7	100	100	100	100
4.0	99	99	99	99
4.6	90	99	99	99
5.2	20	92	99	99
5.9	0	50	95	99
6.3	0	0	76	98
6.5	0	0	35	93
7.3	0	0	0	64

TABLE 2

Percent Suprofen in Suspension					
pH	Concentration of Suprofen in the Formulation .001	.01	.1	1.0	5.0
4.0	0	0	77	98	99
5.0	0	0	45	95	99
6.0	0	0	0	54	95
7.0	0	0	0	0	68

appropriate for treating a wide range of conditions that require therapeutic treatment as well as inflammation.

Non-steroidal anti-inflammatory agents as used herein are intended to mean any non-narcotic analgesic/non-steroidal anti-inflammatory compound useful as a cyclooxygenase inhibitor. Preferably the non-steroidal anti-inflammatory agent is one or more of the following: aspirin, benoxaprofen, benzofenac, bucloxic acid, butibufen, carprofen, cicloprofen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, flurbiprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketroprofen, lactorolac, lonazolac, metiazinic, miroprofen, naproxen, oxaprozin, oxepinac, phenacetin, pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, and zomepirac. Preferably, the agent is selected from the group consisting of diclofenac, suprofen, and flurbiprofen sodium and mixtures thereof. More preferably, the non-steroidal anti-inflammatory agent is diclofenac sodium.

The pH and concentration of the agent in the formulation are selected to provide sufficient drug in solution to begin effective therapeutic treatment but at least some in suspension to serve as a depot for the agent which delays release of that agent over time. The pH of the aqueous mixture may be about 4.0 to about 8.0 and preferably, about 5.0 to about 6.8, but at a level sufficient to establish the desired suspension amount of non-steroidal anti-inflammatory agent.

The composition may be formulated as an aqueous suspension. The composition may contain water soluble polymers or water insoluble polymers as the suspending agent. Examples of such soluble polymers are cellulosic polymers like hydroxypropyl methylcellulose. Water insoluble polymers are preferably crosslinked carboxy-vinyl polymers. It is important to note, however, that the present invention requires the drug to be in suspension without reference to whether the polymer is or is not in suspension.

using appropriate amounts of physiologically and ophthalmologically acceptable salts. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the aqueous suspension, will give osmolalities within the above-stated ranges. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges. Sugars like mannitol, dextrose, glucose or other polyols may be added to adjust osmolarity.

The amounts of insoluble lightly crosslinked polymer particles, the pH, and the osmotic pressure chosen from within the above-stated ranges will be correlated with each other and with the degree of crosslinking to give aqueous suspensions having viscosities ranging from about 500 to about 100,000 centipoise, and preferably from about 5,000 to about 30,000 or about 5,000 to about 20,000 centipoise, as measured at room temperature (about 25°C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. Formulations of the present invention should have a viscosity that is suited for the selected route of administration. Viscosity up to about 30,000 = drop. About 30,000 to about 100,000 centipoise is an advantageous viscosity range for ophthalmic administration in ribbon form.

When water soluble polymers are used, such as hydroxypropyl methylcellulose, the viscosity will typically be about 10 to about 400 centipoises, more typically about 10 to about 200 centipoises or about 10 to about 25 centipoises.

The composition of the present invention will ordinarily contain surfactants and, if desired, adjuvants, including additional medicaments, buffers, antioxidants, tonicity adjusters, preservatives, thickeners or viscosity modifiers,

contact with tear fluid. For instance, when a formulation containing DuraSite® is administered to the eye at a lower pH, the DuraSite® system swells upon contact with tears. This gelation or increase in gelation leads to entrapment of the suspended drug particles, thereby extending the residence time of the composition in the eye. The drug is released slowly as the suspended particles dissolve over time as the solubility of the drug is higher in the tear fluid. All these events eventually lead to increased patient comfort, increase in the time the drug is in contact with the eye tissues, thereby increasing the extent of drug absorption and duration of action of the formulation in the eye.

Although described above in the context of viscous aqueous polymeric suspensions containing non-steroidal anti-inflammatory in solution and in suspension, the compositions of this invention can be formulated in any other suitable manner. For example, diclofenac sodium may be dissolved and added by sterile filtration to a preparation containing sodium chloride, hydroxypropyl methyl cellulose and surfactant. This mixture may then be adjusted to the appropriate pH by known techniques, for example by the addition of sodium hydroxide. Other methods will be apparent to one skilled in the art.

In general, ophthalmic formulations suitable for topical ophthalmic administration may be formulated and administered in accordance with techniques familiar to persons skilled in the art. The finished formulations are preferably stored in opaque or brown containers to protect them from light exposure, and under an inert atmosphere. These aqueous suspensions can be packaged in preservative-free, single-dose non-reclosable containers. This permits a single dose of the medicament to be delivered to the eye as a drop or ribbon, with the container then being discarded after use. Such containers eliminate the potential for preservative-related irritation and sensitization of the corneal epithelium, as has been observed to occur particularly from ophthalmic medicaments containing mercurial preservatives. Multiple dose containers can also be used, if desired, particularly since the relatively low viscosities of the aqueous suspensions of this invention permit constant, accurate dosages to be

TABLE 4 (continued)

COMPONENTS	Example 6	Example 7	Example 8	Example 9	Example 10
Diclofenac Sodium	1.0	0.01	1.0	0.01	1.0
Noveon AA-1	1.3	1.3	1.3	1.3	1.3
Hydroxypropyl Methylcellulose	-	-	-	-	-
Edetate Sodium	0.1	0.1	0.1	0.1	0.1
Sodium Chloride	-	-	-	0.5	0.5
Mannitol	-	-	-	1	1
Dextrose	2.8	-	-	-	-
o-Phosphoric Acid	-	0.5	0.5	-	-
Sodium Borate	-	0.5	0.5	-	-
Pluronic F127	0.2	0.05	0.2	0.05	0.2
Sodium Hydroxide	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

TABLE 5

COMPOSITION	Example 11	Example 12	Example 13	Example 14
Suprofen	1.0	2.0	-	-
Flurbiprofen Sodium	-	-	1.0	0.1
Noveon AA-1	1.3	1.3	1.3	1.3
Edetate Sodium	0.1	0.1	0.1	0.1
Sodium Chloride	0.5	0.5	0.5	0.5
Mannitol	1	1	1	1
Pluronic F127	0.2	0.05	0.2	0.05
Sodium Hydroxide	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA) is then added to the polymer suspension and stirred for 10 minutes. The polymer suspension is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121°C for 20 minutes. Dextrose is dissolved in 1/10 of the final weight of water and sterile filtered (0.22 μm filter) in to the polymer suspension and stirred for 10 minutes. Diclofenac sodium is dissolved separately in approximately 1/2 of the final weight of water, added to the polymer mixture by sterile filtration and stirred for 10 minutes. The mixture is adjusted to pH 6.0 with 10N sodium hydroxide, brought to final weight with water and surfactant by sterile filtration and aseptically filled into unit-dose containers.

Examples 7-8

Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA), o-phosphoric acid, and sodium borate are then added to the polymer suspension and stirred for 10 minutes after each addition. The polymer solution is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121° for 20 minutes. Diclofenac sodium is dissolved separately in approximately 1/2 of the final weight of water, added to the polymer mixture by sterile filtration (0.22 μm filter) and stirred for 10 minutes. The mixture is adjusted to pH 6.0 with 10N sodium hydroxide, brought to final weight with water and surfactant by sterile filtration and aseptically filled into unit-dose containers.

Examples 9-10

Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs. with an

of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

12. A composition for topical treatment of the eye comprising: an aqueous suspension of a non-steroidal anti-inflammatory agent, said composition having a pH of about 4.0 to about 6.8, and containing from about 0.1% to about 6.5% by weight based on the total weight of the suspension of a crosslinked carboxyl-containing polymer, and wherein a therapeutic amount of about 10% - 99% of said agent is in suspension and a therapeutic amount of said agent is in solution.

13. A composition as recited in claim 12 wherein said agent is selected from the group consisting of diclofenac, suprofen, flurbiprofen and mixtures thereof.

14. A composition as recited in claim 13 wherein said agent is diclofenac.

15. A composition as recited in claim 14 wherein said diclofenac is about 0.1 to about 1.0% by weight of the composition.

16. A composition as recited in claim 9 wherein said polymer is about 0.1 to about 1.3% by weight of the suspension.

17. A composition as recited in claim 14 having a viscosity of about 5,000 to about 30,000 centipoises.

18. A composition as recited in claim 15 having a viscosity of about 5,000 to about 20,000 centipoises.

19. A method for treating eye inflammation comprising the step of: applying to an eye an amount of an aqueous suspension of diclofenac effective to treat the eye, said composition having a pH of about 4.0 to about 8.0 and a concentration of diclofenac wherein at least some of said diclofenac is in suspension and some is in solution.

20. A method for treating the eye comprising the step of: applying to an eye an amount of an aqueous suspension of diclofenac effective to treat the eye, said composition having a pH of about 5.0 to about 6.8 and a concentration of diclofenac wherein about 70% - 99% of said diclofenac is in suspension and the remainder is in solution.

INTERNATIONAL SEARCH REPORT

Inter. ...al Application No
PCT/US 95/06192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/10 A61K31/19 A61K31/38 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INT. J. PHARMACEUT., vol. 55, no. 2-3, 1989 pages 123-128, VULOVIC ET AL. 'Some studies into the properties of indomethacin suspensions intended for ophthalmic use' * see whole document * ---	1-3,7,8, 21
X	US-A-4 559 343 (HAN ET AL.) 17 December 1985 * see col. 3-4, claims * ---	1,2,4, 7-11,21
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ... nal Application No
PCT/US 95/06192

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